REMARKS

A. Summary of the Claimed Invention

Broadly, the invention of the subject application is directed to a method for detecting the presence of one or more specific nucleotides at a predetermined target position in a target nucleic acid.

The method of the invention includes the step of providing an analyzable amount of the target nucleic acid in a single stranded form. The method further includes the step of hybridizing the target nucleic acid with a detection primer to form a target-nucleic-acid/detection-primer hybrid. The detection primer comprises a detection-primer nucleotide sequence, which has a primer-extension-initiation 3'-end nucleotide that constitutes a 3' end of the detection primer. The detection-primer nucleotide sequence is complementary to a primer-hybridizing nucleotide sequence of the target nucleic acid. A nucleotide in the target nucleic acid complementary to the primer-extension-initiation 3'-end nucleotide of the detection-primer nucleotide sequence defines a primer-end complement nucleotide. The primer-hybridizing nucleotide sequence of the target nucleic acid extends towards the 3' end of the target nucleic acid from the primer-end complement nucleotide. The primer-end complement nucleotide is located in the target nucleic acid at a position 3'-ward of the predetermined target position. The position of the primer-end complement nucleotide is subject to a constraint that no nucleotide of the same type as the one or more specific nucleotides to be detected be located in the target nucleic acid in any position between the position of the primer-end complement nucleotide and the predetermined target position.

The method of the invention for detecting the presence of one or more nucleotides at a target position in a target nucleic acid further includes the step of forming an extension-reaction mixture by exposing the target-nucleic-acid/detection-primer hybrid to an admixture of a polymerization agent and a plurality of nucleoside triphosphates. The nucleoside triphosphates of the admixture include at least one deoxynucleotide and at least one chain-terminating nucleotide analogue. Each deoxynucleotide of the admixture of nucleotides triphosphates is

complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the admixture is complementary.

In one aspect, the plurality of nucleotide triphosphates of the admixture is such that, if a deoxynucleotide is complementary to a specific nucleotide at the predetermined target position, a detectable nucleotide-identifier primer-extension product is formed of the detection primer extended to include an extension portion incorporating the deoxynucleotide. In a second aspect, the plurality of nucleoside triphosphates of the admixture is such that, if a chain-terminating nucleotide analogue is complementary to a specific nucleotide at the predetermined target position, a detectable nucleotide-identifier primer-extension product is formed of the detection primer extended to include an extension portion terminated with the chain-terminating nucleotide analogue. In both aspects, the detectable nucleotide-identifier primer-extension product is detectably different from the detection primer and from any alternative primer-extension product which would be formed if a nucleotide other than said specific nucleotide were at the target position.

Finally, method of the invention for detecting the presence of one or more nucleotides at a target position in a target nucleic acid includes the step of analyzing the extension-reaction mixture for the presence or absence of the detectable nucleotide-identifier primer-extension product to detect the presence of the corresponding specific nucleotide at the target position in the target nucleic acid.

B. Summary of the Outstanding
Office Action

In the Office Action of 21 July 2004, claim 98 was rejected under 35 USC §112, second paragraph, with the assertion that the claim was indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regarded as the invention. It was noted in the Office Action that the claim called for selecting a "deoxyribonucleotide" from "ddATP,

ddGTP, ddCTP, and ddTTP," but that ddATP, ddGTP, ddCTP, and ddTTP were in fact dideoxyribonucleotides.

Claims 83, 86, 88 through 94 inclusive, 96, 98, 100, and 101 were rejected under 35 USC §112, first paragraph, in the outstanding Office Action with the assertion that the claims contained subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. With respect to the rejection under 35 USC §112, first paragraph, it was asserted that claims 83, 86, 88 through 94 inclusive, 96, 98, 100, and 101 were not supported by the specification and introduced new matter to the claims. With respect to claim 83, it was asserted that the claim was drawn to a method for identifying a nucleotide at a predetermined site by hybridizing a detection primer whose 3' terminus hybridizes to nucleotide 3'-ward of the predetermined site, such that no nucleotide of the same type as the one or more specific nucleotides to be detected is located in the target in any position between the position of the 3' terminus of the primer and the predetermined target position, and extending the primer in the presence of at least one deoxynucleotide and a chain-terminating nucleotide, such that, if a deoxynucleotide is complementary to a specific nucleotide at the predetermined position, a "detectable nucleotide identifier primer extension product" would be formed, which would be detectably different from the detection primer and any alternative primer extension product which would be formed if a nucleotide other than the specific nucleotide were at the target position. It was asserted that claim 86 was drawn to the same method, wherein the primer is extended in the presence of at least one deoxynucleotide and a chain-terminating nucleotide analog, such that if the chain-terminating nucleotide analog were complementary to a specific nucleotide at the predetermined position, a "detectable nucleotide identifier primer extension product" would be formed which would be detectably different from the detection primer and any alternative primer extension product, which would be formed if a nucleotide other than the specific nucleotide were at the target position. It was asserted that the specification of the subject application did not describe methods, wherein neither the deoxynucleotide nor the dideoxynucleotide was labeled directly or indirectly, as defined at page

7, lines 1 through 5. It was asserted that the specification did not describe a method wherein extension occurred in the presence of at least one deoxynucleotide and one or more chain-terminating oligonucleotides, wherein neither the deoxynucleotide nor the chain terminator was detectably labeled as now encompassed by the claims. It was asserted that the specification did not support the method of independent claims 83 and 86, or of dependent claims 88 through 94, 96, 98, 100, and 101, which are dependent on claims 83 or 86, which encompasses a primer extended in the presence of deoxynucleotide or chain terminator, which may or may not be labeled.

It was noted in the outstanding Office Action in connection with the rejection of claims 83, 86, 88 through 94 inclusive, 96, 98, 100, and 101 under 35 U.S.C. 112, first paragraph, that in a prior response submitted on behalf of the applicants it was pointed out that claims 82 through 101 inclusive of the application found support at page 7, lines 10 through 12, which state that "[t]he method of detection of the variable nucleotide(s) is based on primer extension and incorporation of detectable nucleoside triphosphates in the detection step." It was further pointed out in the applicants' previous response that the quoted passage did not require that the "detectable nucleoside triphosphates" be labeled and that the term "labeled nucleoside triphosphate," but not the term "detectable nucleoside triphosphate," was expressly defined at page 17, lines 1 through 5 of the specification. It was asserted in the outstanding Office Action that since the specification did not expressly define the term "detectable nucleoside triphosphate," the term would have been interpreted in the context of the teachings of the rest of the specification. It was asserted that the quoted passage, when read in the context of the paragraph immediately following it, set forth that the methods of the invention required labeled nucleoside triphosphates. It was asserted that it was unclear what a detectable nucleoside triphosphate would be other than one which was labeled directly or indirectly, as exemplified by, assertedly, the rest of the teachings of the specification. It was asserted that because the term "detectable nucleoside triphosphate" was not specifically defined by the specification, when considering the term with the teachings of the specification as a whole, the detection of a primer extension product which incorporated a nucleoside triphosphate other than a labeled nucleoside

triphosphate as defined in the specification was assertedly never suggested. It was asserted that the specification did not provide support for a nucleoside triphosphate which was not either "labeled with a detectable moiety or modified so as to comprise an attachment moiety capable of binding a detectable label."

Claims 82 through 101 inclusive were rejected in the Office Action of 21 July 2004 under the doctrine of obviousness-type double patenting as assertedly unpatentable over claims 1 through 26 inclusive of United States patent No. 6,013,431 ("the '431 patent"). Although it was conceded in the Office Action that the conflicting claims were not identical, it was asserted that the conflicting claims were not patentably distinct from one another because the claims of the subject application contained overlapping subject matter with the claims of the '431 patent. It was asserted that the claims of the '431 patent were drawn to a method for determining a nucleotide variation at a defined site using a primer which hybridized at its 3' end to the nucleotide flanking the nucleotide variation and extending in the presence of a mixture containing at least one labeled deoxynucleotide and at least one dideoxynucleotide. It was asserted that the claims of the subject application were drawn to the same method assertedly in which extension occurred in the presence of a mixture containing at least one deoxynucleotide and one or more chain terminating nucleotide analogues in which the deoxynucleotide or chain terminator nucleotide might or might not be labeled. It was asserted that because the claims of the subject application and those of the '431 patent both included a method in which the deoxynucleotide was labeled, the claims of the '431 patent and the claims of the subject application contained overlapping subject matter.

C. Summary of the Present Amendments
and Request for Reconsideration

Claim 98 has been amended in the present reply to substitute the term --dideoxyribonucleotide-- for the term "deoxyribonucleotide." The amendment to claim 98 finds support in the specification of the application as filed, for example, at page 23, lines 13 through

25, and page 34, lines 7 through 12. It is submitted that the amendment to claim 98 does not constitute new matter.

With regard to the double patenting rejection involving the '431 patent, a terminal disclaimer in the style of form PTO/SB/26 is being submitted with the present reply disclaiming the terminal part of the statutory term of any patent granted on the subject application which would extend beyond the expiration date of the full statutory term of the prior '431 patent as defined in the form.

Reconsideration of the subject application as amended above in light of the comments below is respectfully requested.

D. The Rejection Under 35 U.S.C. § 112,
First Paragraph

The attorneys for the applicants maintain that there is ample support in the specification of the subject application as originally filed for claims 82 through 101 inclusive of the application as amended, specifically including claims 83, 86, 88 through 94 inclusive, 96, 98, 100, and 101.

As pointed out in the prior response of 29 March 2004, at page 7, lines 10 through 12 of the subject application as filed in the section entitled "Summary of the Invention," it is stated that:

> The method of detection of the variable nucleotide(s) is based on primer extension and incorporation of detectable nucleoside triphosphates in the detection step. By selecting the detection step primers from the region immediately adjacent to the variable nucleotide, this variation can be detected after incorporation of as few as one nucleoside triphosphate.

The quoted description of the invention in the application as filed does not require that the "detectable nucleoside triphosphates" incorporated in the detection step of the method for detecting variable nucleotide(s) of the invention be labeled with a detectable label or be modified to include an attachment moiety capable of binding a detectable label. At page 17, lines 1

through 5 of the application as originally filed, the term "labelled nucleoside triphosphate" – not the term "detectable nucleoside triphosphate" used in the description of the invention quoted above – is expressly defined to refer to a nucleoside triphosphate labeled with a detectable label or modified to comprise an attachment moiety capable of binding a detectable label. [Underlining added.] A person skilled in the art as of the effective filing date of the subject application with the specification of the application at hand would have concluded, it is submitted, that the expression "detectable nucleoside triphosphate" as used in the subject application was not limited to the particular definition set out in the specification for the expression "labelled nucleoside triphosphate" since the defined expression "labelled nucleoside triphosphate" could have been used in the passage quoted above, but the expression "detectable nucleoside triphosphate" was used instead.

Independent claim 83 of the subject application is directed to a method for detecting the presence of one or more specific nucleotides at a predetermined target position in a target nucleic which includes the step, among others, of forming an extension-reaction mixture by exposing a target-nucleic-acid/detection-primer hybrid to an admixture of a polymerization agent and a plurality of nucleoside triphosphates. The nucleoside triphosphates of the admixture include at least one deoxynucleotide and at least one chain-terminating nucleotide analogue. Each deoxynucleotide of the admixture of nucleotides triphosphates is complementary to a nucleotide which differs from any nucleotide to which a chain-terminating nucleotide analogue of the admixture is complementary. The plurality of nucleotide triphosphates of the admixture of the method of claim 83 is specified to be such that, if a deoxynucleotide is complementary to a specific nucleotide at the predetermined target position, a detectable nucleotide-identifier primer-extension product is formed of the detection primer extended to include an extension portion incorporating the deoxynucleotide. The detectable nucleotide-identifier primer-extension product is specified to be detectably different from the detection primer and from any alternative primer-extension product which would be formed if a nucleotide other than said specific nucleotide were at the target position.

It is submitted that independent claim 83 is supported by the specification of the subject application as originally filed.

Reasoning analogous to that applied above to claim 83 applies with respect to independent claim 86 and that therefore claim 86 is supported by the specification of the subject application as originally filed as well.

Claims 88 through 94 inclusive, 96, 98, 100, and 101 are dependent claims which depend upon either of independent claims 83 or 86. It is submitted that each of claims 88 through 94 inclusive, 96, 98, 100, and 101 finds support in the subject application as originally filed.

For the reasons set forth above, it is submitted that each of claims 83, 86, 88 through 94 inclusive, 96, 98, 100, and 101 finds support in the subject application as filed and does not constitute new matter that the rejection of the claims under 35 USC §112, first paragraph, was unwarranted and should be withdrawn.

E. The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 98 has been amended in the present response with the comments in mind concerning the rejection of the claim under 35 USC §112, second paragraph. It is submitted that, particularly as amended, claim 98 meets the standards of 35 USC §112, second paragraph, and that rejection of the claim under that statutory provision should be withdrawn.

F. The Double-Patenting Rejection

Although the attorneys for the applicants maintain that pending claims 82 through 101 inclusive of the subject application are patentable over claims 1 through 26 inclusive of the '431 patent with regard to the doctrine of obviousness-type double patenting, in order to expedite prosecution of the application, a terminal disclaimer in the style of form PTO/SB/26 is being submitted with the present reply disclaiming the terminal part of the statutory term of any patent granted on the subject application which would extend beyond the expiration date of the full

statutory term of the prior '431 patent as defined in the form. It is submitted that the accompanying terminal disclaimer obviates the double patenting rejection of claims 82 through 101 inclusive and that the double patenting rejection should therefore be withdrawn.

G. Conclusion

For the reasons set forth above, it is submitted that the claims of the subject application as amended fully meet the standards of 35 U.S.C. § 112, first and second paragraphs, and that the obviousness-type double patenting rejection of the outstanding Office Action with respect to the prior '431 patent has been obviated. Early allowance of the application is therefore earnestly solicited.

Respectfully submitted,

Attorneys for the Applicants

by _____
J. David Ellett, Jr.
Reg. No. 27,875

Telephone No.: (212) 813-1600